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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/551,105	09/26/2005	**Jeffrey Allen Whitsett**	CHM-003	4312

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EXAMINER	
ROMEO, DAVID S	
ART UNIT	**PAPER NUMBER**
1647	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/551,105	WHITSETT, JEFFREY ALLEN	
	Examiner	Art Unit	
	David S. Romeo	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 July 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,7,8 and 30-41* is/are pending in the application.

4a) Of the above claim(s) *7,8 and 34-41* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3 and 30-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) *1,3,7,8 and 30-41* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 September 2005* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *0606*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed 07/31/2008 has been entered. Claims 1, 3, 7, 8 and 30–41 are pending.

Election/Restrictions

Applicant's election with traverse of group I, claims 1–3 and 30–30, drawn to a composition comprising FGF-18 and of the species Shh in the reply filed on 07/31/2008 is acknowledged. The traversal is on the ground(s) that unity of invention exists because it was not known in the prior art that FGF-18, Shh, β-catenin and Wnt family of proteins were all related in their cartilage forming properties. This is not found persuasive because although the compounds included within the Markush group share the common utility of cartilage formation, they do not share a substantial structural feature disclosed as being essential to that utility. Therefore, unity of invention does not exists.

The requirement is still deemed proper and is therefore made FINAL.

Claims 7, 8 and 34–41 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 07/31/2008.

Drawings

The drawings are objected to as failing to comply with 37 CFR 1.84(p)(5) because they do not include the following reference sign(s) mentioned in the description: For example, the brief description of Fig. 2 (page 9) mentions "C" and "D." However, Fig 2 does not include "C" and "D." See also the brief description of Figs. 4 and 5. Corrected drawing sheets in compliance

with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

The drawings are objected to as failing to comply with 37 CFR 1.84(p)(5) because they include the following reference character(s) not mentioned in the description: C and D in Fig 8; D in Fig. 9; and G and H in Fig 14. Corrected drawing sheets in compliance with 37 CFR 1.121(d), or amendment to the specification to add the reference character(s) in the description in compliance with 37 CFR 1.121(b) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Figures 2–9, 13–16, 18, 19 and 21 are presented with several views, e.g., A-B. However, the brief description of the drawings refers only to Figures 2–9, 13–16, 18, 19 and 21. If the drawings show Figures 1A, 1B, and 1C, for example, and the brief description of the drawings refers only to Figure 1, this is an error in the specification which must be corrected. See MPEP § 601.01(g). The Brief Description of the Drawings must be amended to accordingly.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1 and 30–32 are rejected under 35 U.S.C. 102(b) as being anticipated by Deisher (U. S. Patent No. 6,352,971) in view of GenBank accession number AB007422.

A 35 U.S.C. 102 rejection over multiple references has been held to be proper when the extra references are cited to:

(A) Prove the primary reference contains an "enabled disclosure;"
(B) Explain the meaning of a term used in the primary reference; or
(C) Show that a characteristic not disclosed in the reference is inherent.

MPEP § 2131.01.

Deisher provides an isolated FGF homolog polypeptide and a pharmaceutical composition comprising same, in combination with a pharmaceutically acceptable vehicle (column 4, line 37 through column 5, full paragraph 1; column 26, lines 30-67).

According to the instant specification:

> [0074] As used herein, the terms "FGF-18" and "FGF-18 protein" refer to Fibroblast Growth Factor-18, the polypeptide (FGF-18 protein) that is capable of inducing formation of cartilage. FGF-18 protein (house mouse) has the amino acid sequence shown in SEQ ID NO:2 and GenBank accession number AB004639, while FGF-18 protein (human) has the amino acid sequence shown in SEQ. ID NO:4 and GenBank accession number AB007422.

The only difference between Deisher's FGF homolog polypeptide and FGF-18 (SEQ ID NO: 4) of the present application is the absence of an additional methionine at the N-terminus of Deisher's FGF homolog polypeptide, as indicated in the sequence comparison below:

```
US-09-368-951-2
; Sequence 2, Application US/09368951
; Patent No. 6352971
; SEQ ID NO 2
;   LENGTH: 207
;   TYPE: PRT
;   ORGANISM: Homo sapiens
US-09-368-951-2

  Query Match             99.5%;  Score 1097;  DB 2;  Length 207;
  Best Local Similarity   100.0%;  Pred. No. 5.6e-119;
  Matches  207;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          2 MYSAPSACTCLCLHFLLLCFQVQVLVAEENVDFRIHVENQTRARDDVSRKQLRLYQLYSR 61
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 MYSAPSACTCLCLHFLLLCFQVQVLVAEENVDFRIHVENQTRARDDVSRKQLRLYQLYSR 60

Qy         62 TSGKHIQVLGRRISARGEDGDKYAQLLVETDTFGSQVRIKGKETEFYLCMNRKGKLVGKP 121
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         61 TSGKHIQVLGRRISARGEDGDKYAQLLVETDTFGSQVRIKGKETEFYLCMNRKGKLVGKP 120

Qy        122 DGTSKECVFIEKVLENNYTALMSAKYSGWYVGFTKKGRPRKGPKTRENQQDVHFMKRYPK 181
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        121 DGTSKECVFIEKVLENNYTALMSAKYSGWYVGFTKKGRPRKGPKTRENQQDVHFMKRYPK 180

Qy        182 GQPELQKPFKYTTVTKRSRRIRPTHPA 208
              ||||||||||||||||||||||||||
Db        181 GQPELQKPFKYTTVTKRSRRIRPTHPA 207.
```

Deisher's FGF homolog polypeptide is identical to the amino acid sequence shown in GenBank accession number AB007422. Therefore, Deisher discloses a pharmaceutical composition comprising FGF-18.

Deisher also teaches:

> In general, a therapeutically effective amount of zFGF-5 is an amount sufficient to produce a clinically significant change in myocyte proliferation, heart function, bone formation or increases in specific cell types associated with mesenchymal stem cells and progenitors for myocytes, osteoblasts and chrondocytes. (column 26, lines 54-59).

There is no discernible difference between an amount of Deisher's FGF homolog polypeptide sufficient to produce a clinically significant change in myocyte proliferation, heart function, bone formation or increases in specific cell types associated with mesenchymal stem cells and progenitors for myocytes, osteoblasts and chrondocytes and "an amount effective to induce cartilage formation," as recited in the instant claims. In the absence of evidence to the contrary, Deisher discloses a pharmaceutical composition comprising FGF-18 in an amount effective to induce cartilage formation.

The limitations:

> "wherein the FGF-18 protein is adapted to be administered to an affected area of a patient in an amount effective to induce cartilage formation in the affected area" (claim 30);
>
> "wherein the affected area is a conducting airway" (claim 31); and
>
> "wherein the conducting airway is at least one of the trachea, bronchi, lung and larynx" (claim 32);

do not distinguish over the pharmaceutical composition disclosed by Deisher.

Claim 1 is rejected under 35 U.S.C. 102(e) as being anticipated by Ellsworth (U. S. Publication No. 20040136970).

The effective filing date of Ellsworth is 10/07/2002, which is obtained via U.S. Provisional application No. 60/416,670.

Ellsworth discloses pharmaceutical compositions comprising FGF-18 in an amount effective to induce cartilage formation (paragraphs [0035]-[0041]).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 3 and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ellsworth (U. S. Publication No. 20040136970) as applied to claim 1 above and further in view of Hunziker (U. S. Patent No. 5,270,300) and Warzecha (U. S. Patent No. 7,160,725).

Ellsworth teaches pharmaceutical compositions comprising FGF-18 in an amount effective to induce cartilage formation, as discussed above. Ellsworth also teaches that any growth factor with specificity for chondrocytes lineage cells that stimulates those cells to grow, differentiate or induce cartilage production would be valuable for maintaining, repairing or replacing articular cartilage (page 1, paragraph [0006]).

Hunziker discloses compositions to induce the repair of lesions in cartilage (column 3, last full paragraph). Compounds useful in the compositions include proliferation agents, chemotactic agents and any peptide, polypeptide, protein or any other compound or composition which induces differentiation of cartilage repair cells into chondrocytes, such as TGFs and FGFs, singly or in combination (column 9, line 7 through column 10, line 20).

Warzecha teaches compositions for promoting the growth of chondrocytes or chondrogenic progenitor cells to form a three dimensional cartilage matrix comprising a

hedgehog polypeptide alone or in combination with a TGFβ family member (column 5, line 26 through column 11, line 44; paragraph bridging columns 13-14; column 20, last full paragraph). Exemplary hedgehog polypeptides are provided in SEQ ID NOs: 10-18 and mature forms thereof (column 13, full paragraphs 1-2). Warzecha's SEQ ID NO: 13 is 98% identical to SEQ ID NO: 6 (house mouse Shh) of the instant application (page 14, paragraph [0076]), as indicated in the following sequence comparison:

```
Score =  885 bits (2287),  Expect = 0.0, Method: Compositional matrix adjust.
Identities = 432/437 (98%), Positives = 433/437 (99%), Gaps = 0/437 (0%)

Query  1    MLLLLARCFLVILASSLLVCPGLACGPGRGFGKRRHPKKLTPLAYKQFIPNVAEKTLGAS  60
            MLLLLARCFLVILASSLLVCPGLACGPGRGFGKRRHPKKLTPLAY QFIPNVAEKTLGAS
Sbjct  1    MLLLLARCFLVILASSLLVCPGLACGPGRGFGKRRHPKKLTPLAYLQFIPNVAEKTLGAS  60

Query  61   GRYEGKITRNSERFKELTPNYNPDIIFKDEENTGADRLMTQRCKDKLNALAISVMNQWPG  120
            GRYEGKITRNSERFKELTPNYNPDIIFKDEENTGADRLMTQRCKDKLNALAISVMNQWPG
Sbjct  61   GRYEGKITRNSERFKELTPNYNPDIIFKDEENTGADRLMTQRCKDKLNALAISVMNQWPG  120

Query  121  VRLRVTEGWDEDGHHSEESLHYEGRAVDITTSDRDRSKYGMLARLAVEAGFDWVYYESKA  180
            V+LRVTEGWDEDGHHSEESLHYEGRAVDITTSDRDRSKYGMLARLAVEAGFDWVYY SKA
Sbjct  121  VKLRVTEGWDEDGHHSEESLHYEGRAVDITTSDRDRSKYGMLARLAVEAGFDWVYYGSKA  180

Query  181  HIHCSVKAENSVAAKSGGCFPGSATVHLEQGGTKLVKDLRPGDRVLAADDQGRLLYSDFL  240
            HIHCSVKAENSVAAKSGGCFPGSATVHLEQGGTKLVKDLRPGDRVLAADDQGRLLYSDFL
Sbjct  181  HIHCSVKAENSVAAKSGGCFPGSATVHLEQGGTKLVKDLRPGDRVLAADDQGRLLYSDFL  240

Query  241  TFLDRDEGAKKVFYVIETLEPRERLLLTAAHLLFVAPHNDSGPTPGPSALFASRVRPGQR  300
            TFLDRDEGAKKVFYVI TLEPRE LLLTAAHLLFVAPHNDSGPTPGPSALFASRVRPGQR
Sbjct  241  TFLDRDEGAKKVFYVIGTLEPREPLLLTAAHLLFVAPHNDSGPTPGPSALFASRVRPGQR  300

Query  301  VYVVAERGGDRRLLPAAVHSVTLREEEAGAYAPLTAHGTILINRVLASCYAVIEEHSWAH  360
            VYVVAERGGDRRLLPAAVHSVTLREEEAGAYAPLTAHGTILINRVLASCYAVIEEHSWAH
Sbjct  301  VYVVAERGGDRRLLPAAVHSVTLREEEAGAYAPLTAHGTILINRVLASCYAVIEEHSWAH  360

Query  361  RAFAPFRLAHALLAALAPARTDGGGGGSIPAAQSATEARGAEPTAGIHWYSQLLYHIGTW  420
            RAFAPFRLAHALLAALAPARTDGGGGGSIPAAQSATEARGAEPTAGIHWYSQLLYHIGTW
Sbjct  361  RAFAPFRLAHALLAALAPARTDGGGGGSIPAAQSATEARGAEPTAGIHWYSQLLYHIGTW  420

Query  421  LLDSETMHPLGMAVKSS  437
            LLDSETMHPLGMAVKSS
Sbjct  421  LLDSETMHPLGMAVKSS  437.
```

Accordingly, Warzecha discloses compositions for promoting the growth of chondrocytes or chondrogenic progenitor cells to form a three dimensional cartilage matrix comprising a Shh alone or in combination with a TGFβ family member.

Although none of Ellsworth, Hunziker, or Warzecha taken alone teach a composition comprising FGF-18 and Shh or FGF-18 and a TGFβ family member, Ellsworth and Hunziker recognize that any protein that any protein that stimulates chondrocytes lineage cells that to grow, differentiate or induce cartilage production would be valuable for maintaining, repairing or replacing articular cartilage. Hunziker and Warzecha also recognize that combinations of growth factors, such as TGFs and FGFs or Shh and a TGFβ family member, are useful for cartilage repair. Therefore, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to make a pharmaceutical composition comprising FGF-18 in an amount effective to induce cartilage formation, as taught by Ellsworth, and to modify that composition with a TGFβ family member or Shh with a reasonable expectation of success. One of ordinary skill in the art would be motivated to make this modification because it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose. The idea of combining them flows logically from their having been taught in the prior art either singly or in combination with other cartilage repair proteins.

The limitation "adapted to be administered to the affected area in an amount effective to enhance cartilage growth and patterning" does not distinguish the claimed composition from the composition taught by the prior art.

The invention is prima facie obvious over the prior art.

Conclusion

No claims are allowable.

ANY INQUIRY CONCERNING THIS COMMUNICATION OR EARLIER COMMUNICATIONS FROM THE EXAMINER SHOULD BE DIRECTED TO DAVID S. ROMEO WHOSE TELEPHONE NUMBER IS (571) 272-0890. THE EXAMINER CAN NORMALLY BE REACHED ON MONDAY THROUGH

FRIDAY FROM 9:00 A.M. TO 5:30 P.M. IF ATTEMPTS TO REACH THE EXAMINER BY TELEPHONE ARE UNSUCCESSFUL, THE EXAMINER'S SUPERVISOR, MANJUNATH RAO, CAN BE REACHED AT (571)272-0939.

IF SUBMITTING OFFICIAL CORRESPONDENCE BY FAX, APPLICANTS ARE ENCOURAGED TO SUBMIT OFFICIAL CORRESPONDENCE TO THE CENTRAL FAX NUMBER FOR OFFICIAL CORRESPONDENCE, WHICH IS (571) 273-8300.

CUSTOMERS ARE ALSO ADVISED TO USE CERTIFICATE OF FACSIMILE PROCEDURES WHEN SUBMITTING A REPLY TO A NON-FINAL OR FINAL OFFICE ACTION BY FACSIMILE (SEE 37 CFR 1.6 AND 1.8).

ANY INQUIRY OF A GENERAL NATURE OR RELATING TO THE STATUS OF THIS APPLICATION OR PROCEEDING MAY BE OBTAINED FROM THE PATENT APPLICATION INFORMATION RETRIEVAL (PAIR) SYSTEM. STATUS INFORMATION FOR PUBLISHED APPLICATIONS MAY BE OBTAINED FROM EITHER PRIVATE PAIR OR PUBLIC PAIR. STATUS INFORMATION FOR UNPUBLISHED APPLICATIONS IS AVAILABLE THROUGH PRIVATE PAIR ONLY. FOR MORE INFORMATION ABOUT THE PAIR SYSTEM, SEE HTTP://PAIR-DIRECT.USPTO.GOV. CONTACT THE ELECTRONIC BUSINESS CENTER (EBC) AT 866-217-9197 (TOLL-FREE) FOR QUESTIONS ON ACCESS TO THE PRIVATE PAIR SYSTEM,

/DAVID S ROMEO/
PRIMARY EXAMINER, ART UNIT 1647

DSR
NOVEMBER 9, 2008